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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/501,328	02/09/2000	Michael D. Macklin	7011-0032	3700

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EXAMINER	
SWARTZ, RODNEY P	
ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/501,328	Macklin et al
Examiner	**Art Unit**
Rodney P. Swartz, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *30August2001*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-55* is/are pending in the application.

4a) Of the above, claim(s) *1-6 and 50-55* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *7-49* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *1-55* are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. Applicants' Response to Restriction, received 30August2001, paper#10, is acknowledged.

Applicants elect, without traverse, Invention II, claims 7-49, drawn to method of immunizing, classified in class 424, subclass 9.2.

Claims 1-6 and 50-55 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

2. Claims 7-49 are under consideration.

Drawings

3. This application has been filed with drawings which are acceptable for examination purposes only. The drawings are objected to for the reasons set forth on the attached form PTO-948.

Specification

4. The disclosure is objected to because of the following informalities:

a) page 33, line 28, "from" should be "form",

a) page 33, line 29, "Copenhaga" should be "Copenhagan",

Appropriate correction is required.

5. The specification is objected to because this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. §1.821(a)(1) and (a)(2). However, this application fails to comply with the

requirements of 37 C.F.R. §§1.821(d) "Where the description or claims or a patent application discuss a sequence that is set forth in the 'Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by 'SEQ ID NO:' in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application."

Claim Objections

6. Claims 7-49 are objected to because the claims depend from nonelected claims 1, 2, and 5. Appropriate correction is required.

7. Claim 26 is objected to because of the following informality: line 1, "thecore" should be "the core". Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 8, 9, 12, 16, 17, 20, 30, 31, 34, 42, 43, and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to a "secondary composition" which is used in a boosting step wherein the "secondary composition" comprises "protein antigen" or "live attenuated vaccine". It is unclear: 1) what is the identity of the "protein antigen" or "live attenuated vaccine" , and 2) if these are not obtained from *M. tuberculosis*, how can they be a "boosting step" to the primary administration of a vector which comprises an isolated polynucleotide encoding a plurality of *M. tuberculosis*?

11. Claims 37-49 are rejected under 35 U.S.C. 112, second paragraph, because claim 37 recites the limitation "a vector according to claim 5" in line 3. There is insufficient antecedent basis for this limitation in the claim as claim 5 does not recite "a vector".

12. Claims 13, 14, 21, 22, 35, 36, 47, 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 13, 21, 35, and 47 recite that the live attenuated vaccine is derived from a "*M. tuberculosis* species". It is unclear what is meant by this because *M. tuberculosis* is itself one species.

Claims 14, 21, 22, 36, and 48 recite that the live attenuated vaccine derived from a *M. tuberculosis* species is BCG. It is unclear what is meant by this because BCG is an attenuated

form of *M. bovis* (A. Calmette, C. Guerin, B. Weill-Halle, avec la collaboration de A. Boquet, L Negre, M. Leger, "Essais d'immunisation contre l'infection tuberculeuse", Bull. Acad. Natl. Med. (1924) Vol. 91, pages 787-796).

13. Claims 7-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for composition comprising individual specific vectors comprising individual specific DNA encoding specific *M. tuberculosis* antigens, does not reasonably provide enablement for any and all other combinations of *M. tuberculosis* antigens in a single vector. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The nature of the invention - The instant claims are drawn to a method for eliciting an immune response against *M. tuberculosis* in a subject comprising administering to the subject **a** vector comprising isolated polynucleotide encoding a plurality of *M. tuberculosis* antigens.

The state of the prior art - eliciting immune responses to DNA or antigens of *M. tuberculosis* is well known.

The presence or absence of working examples - The specification teaches that the nucleotide sequences for ten different *M. tuberculosis* antigens were inserted into WRG7054 expression vectors and that various combinations of these ten resulting *M. tuberculosis* antigen constructs were used to form "cocktail" compositions for the vaccination studies.

The specification does not teach the claimed invention, i.e., *M. tuberculosis* DNA encoding a plurality of antigens in "a", i.e., single, vector. Because of the lack of teaching and examples of such a single vector, the claimed invention merely constitutes an invitation to experiment without a reasonable expectation of success.

14. Claims 7-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for alterations in weight, bacterial load, and tissue pathology in guinea pigs, does not reasonably provide enablement for eliciting an immune response as defined in the specification. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or

guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The nature of the invention - method of eliciting an immune response in a subject against *M. tuberculosis* comprising administration of a vector or naked DNA.

The amount of direction or guidance present - The specification defines "immune response" as "the development in an individual of a humoral and/or a cellular immune response to that antigen. For purposes of the present invention, a 'humoral immune response' refers to an immune response mediated by antibody molecules, while a 'cellular immune response' is one medicated by T-lymphocytes and/or other white blood cells." (Page 9, lines 13-17).

The specification teaches that the nucleotide sequences for ten different *M. tuberculosis* antigens were inserted into WRG7054 expression vectors and that various combinations of these ten resulting *M. tuberculosis* antigen constructs were used to form "cocktail" compositions for the vaccination studies. Following administration of these vectors into guinea pigs, the hosts show changes in weight, tissue pathology, and bacterial loads. The specification is silent concerning the parameters which constitute an "immune response", i.e., development of humoral and/or cellular immune response to the antigen administrated.

15. Claims 7-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for alterations in weight, bacterial load, and tissue pathology in guinea pigs, does not reasonably provide enablement for eliciting an immune response in humans. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The nature of the invention - method of eliciting an immune response in a subject against *M. tuberculosis* comprising administration of a vector or naked DNA.

The state of the prior art - The history of vaccination in humans against *Mycobacterial* disease is notorious for a lack of successful protection. In addition, at the time of filing of the instant specification, there remained a lack of correlation of success in animal models with successful vaccination of humans against mycobacterial disease, as evidenced by the review article, "Evaluation of the Protective Potency of New Tuberculosis Vaccines", *Review of Infectious Diseases*, Vol. 11, Supplement 2, pages S484-S490, March-April 1989.

The amount of direction or guidance present - the specification teaches only examples of vaccinating agents using guinea pigs. The specification teaches that the nucleotide sequences for ten different *M. tuberculosis* antigens were inserted into WRG7054 expression vectors and that

various combinations of these ten resulting *M. tuberculosis* antigen constructs were used to form "cocktail" compositions for the vaccination studies. Following administration of these vectors into guinea pigs, the hosts show changes in weight, tissue pathology, and bacterial loads. There are no examples of human subjects.

The quantity of experimentation necessary - Based upon a lack of success in humans concerning tuberculosis vaccines and a lack of correlation of success in animal models with human success, the breadth of the claims constitutes merely an invitation to experiment without a reasonable expectation of success.

16. Claims 8-13, 16-21, 30-35, and 42-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for alterations in weight, bacterial load, and tissue pathology in guinea pigs following administration of vectors and a secondary boosting composition of BCG, does not reasonably provide enablement for boosting steps using secondary compositions commensurate in scope with the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of

experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The nature of the invention - method of eliciting an immune response further comprising administration of ≥1 secondary composition in a boosting step, wherein said secondary composition comprises ≥1 antigen, ≥1 *M. tuberculosis* culture filtrate protein, ≥1 isolated subunits of *M. tuberculosis* proteins, any live attenuated vaccine, or any live attenuated vaccine derived from a *M. tuberculosis* species.

The specification teaches administration of only BCG as a secondary "boosting" composition, i.e., Group Cb. The specification is silent concerning the other claimed "boosting" compositions. Thus, the claimed invention constitutes merely an invitation to experiment without a reasonable expectation of success.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 7-11 and 15-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowrie et al (*Vaccine*, 15(8):834-838, 1997).

The instant claims are drawn to a method of eliciting an immune response against *M. tuberculosis* in a subject, said method comprising administering to the subject a composition comprising ≥2 polynucleotides, wherein each polynucleotide encodes one *M. tuberculosis* antigen, or a composition comprising a vector comprising a polynucleotide which encodes a plurality of *M. tuberculosis* antigens.

Lowrie et al teach such a method using plasmids comprising polynucleotides encoding various *M. tuberculosis* antigens (abstract; Figure 2; page 837, col. 1). Lowrie et al teach a primary immunization followed by booster injections (abstract; Figure 2; page 837, col. 1). Lowrie et al do not teach a composition of either a single plasmid comprising ≥2 polynucleotides or a composition of multiple plasmids, but compositions of single plasmids comprising individual polynucleotides encoding individual *M. tuberculosis* antigens. However, Lowrie et al do suggest multiantigen plasmid vaccines when they state that "For example, a vaccine that gives protection equal to BCG by endogenous expression of only a few proteins will leave the majority of the species specific antigens available for diagnostic tests in vaccinated populations." (Page 837, column 2, lines 11-15).

There, it would have been obvious at the time the invention was made to a person having ordinary skill in the art of DNA vaccination against *M. tuberculosis* to follow the suggestions of Lowrie et al and elicit immune responses against *M. tuberculosis* using compositions comprising ≥2 polynucleotides, wherein each polynucleotide encodes one *M. tuberculosis* antigen, or a

single vector which comprises a polynucleotide which encodes a plurality of *M. tuberculosis* antigens.

19. Claims 23, 25-33, and 37-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowrie et al (*Vaccine*, 15(8):834-838, 1997) in view of Sanford et al (U.S. Pat. No. 5,100,792).

The instant claims are drawn to a method of eliciting an immune response against *M. tuberculosis* in a subject, said method comprising administering to the subject a composition comprising ≥2 polynucleotides, wherein each polynucleotide encodes one *M. tuberculosis* antigen, or a composition comprising a vector comprising a polynucleotide which encodes a plurality of *M. tuberculosis* antigens. The compositions further comprise a core carrier coated with the vectors, and are delivered using a particle-mediated delivery technique.

Lowrie et al teach such a method using plasmids comprising polynucleotides encoding various *M. tuberculosis* antigens (abstract; Figure 2; page 837, col. 1). Lowrie et al teach a primary immunization followed by booster injections (abstract; Figure 2; page 837, col. 1). Lowrie et al do not teach a composition of either a single plasmid comprising ≥2 polynucleotides or a composition of multiple plasmids, but compositions of single plasmids comprising individual polynucleotides encoding individual *M. tuberculosis* antigens. However, Lowrie et al do suggest multiantigen plasmid vaccines when they state that "For example, a vaccine that gives protection equal to BCG by endogenous expression of only a few proteins will leave the majority

of the species specific antigens available for diagnostic tests in vaccinated populations." (Page 837, column 2, lines 11-15).

Therefore, it would have been obvious at the time the invention was made to a person having ordinary skill in the art of DNA vaccination against *M. tuberculosis* to follow the suggestions of Lowrie et al and elicit immune responses against *M. tuberculosis* using compositions comprising ≥2 polynucleotides, wherein each polynucleotide encodes one *M. tuberculosis* antigen, or a single vector which comprises a polynucleotide which encodes a plurality of *M. tuberculosis* antigens.

Lowrie et al do not teach a transdermal delivery system utilizing a core carrier coated with the vectors wherein the carriers are administered using a particle-mediated delivery technique.

Sanford et al teach such a transdermal delivery system utilizing a core carrier (Col. 5, line 31 to col. 14, line 39).

Therefore, it would have been obvious at the time the invention was made to a person having ordinary skill in the art of DNA vaccination against *M. tuberculosis* to utilize the compositions taught and suggested by Lowrie et al, and to delivery the compositions using the delivery system taught by Sanford et al in order to achieve the most efficacious and cost effective means of immunization.

References Deemed Relevant

20. See Attached form PTO-892 for the list of references deemed relevant to the instantly claimed inventions, but not utilized in the rejections.

Conclusion

21. No claims are allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rodney P. Swartz, Ph.D., whose telephone number is (703) 308-4244. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4:00 PM EST.

If attempts to reach the Examiner by telephone are unsuccessful, the examiner's supervisor, Lynette F. Smith, can be reached on (703)308-3909. The facsimile telephone number for the Art Unit Group is (703)308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703)308-0196.

RODNEY P SWARTZ, PH.D
PRIMARY EXAMINER
Art Unit 1645

November 16, 2001